PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Richard G. Langlois et al	Examiner: Nelson C. Yang
Serial No.: 10/643,797	Art Unit: 1641
Filed: 08/19/2003	Attorney Docket No.: IL-11052
TITLE: SYSTEM FOR AUTONOMOUS MONITORING OF BIOAGENTS	

Honorable Commissioner for Patents
Alexandria, VA 22313-1450

Attention: Board of Patent Appeals and Interferences

Dear Sir:

APPELLANTS' BRIEF (37 C.F.R. § 1.192)

This brief is submitted in support of Appellants' Notice of Appeal from the Office Action mailed November 14, 2008 rejecting claims 1-5, 12, 15-16, 19, 27, 29, and 31-40 of the subject application. Appellants' filed two (2) earlier Appeal Briefs, one on January 22, 2008 and the other on August 15, 2008. Prosecution was reopened after Appellants filed the two earlier Appeal Briefs.

Appellants have the option of (1) filing a Reply or (2) filing a New Appeal. Appellants elect option (2) filing a New Appeal. Appellants' Notice of Appeal was filed November 19, 2008. One copy of the brief is being transmitted per 37 C.F.R. § 41.37.

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I. REAL PARTY IN INTEREST

The real party in interest is:

Lawrence Livermore National Security, LLC and the United States of America as represented by the United States Department of Energy (DOE) by virtue of an assignment by the inventor as duly recorded in the Assignment Branch of the U.S. Patent and Trademark Office.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF CLAIMS

The application as originally filed contained claims 1-50.

The claims on appeal are claims 1-5, 12, 15-16, 19, 27, 29, and 31-40.

The status of all the claims in the proceeding (*e.g.*, rejected, allowed or confirmed, withdrawn, objected to, canceled) is:

Claims 41-50 are withdrawn from consideration.

Claims 6-11, 13-14, 17-18, 20-26, 28, and 30 are cancelled.

Claims 1-5, 12, 15-16, 19, 27, 29, and 31-40 are rejected.

Claims 1-5, 12, 15-16, 19, 27, 29, and 31-40 on appeal are reproduced in the Appendix.

IV. STATUS OF AMENDMENTS

There have been no amendments filed subsequent to the January 22, 2008 Appeal Brief, the August 15, 2008 Appeal Brief, or the Office Action mailed November 14, 2008.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Appellants' claimed invention provides an autonomous monitoring apparatus for monitoring air for bioagents wherein the air may contain potential bioagent particles. One embodiment of Appellants' claimed invention is the

Autonomous Pathogen Detection System (APDS) which is described in paragraph [0006] Appellants' original specification on page 4, lines 26-27 and page 5, lines 1-11 as follows:

> "The Autonomous Pathogen Detection System (APDS) is file-cabinet-sized machine that sucks in air, runs tests, and reports the results itself. APDS integrates a flow cytometer and real-time PCR detector with sample collection, sample preparation, and fluidics to provide a compact, autonomously operating instrument capable of simultaneously detecting multiple pathogens and/or toxins. The system is designed for fixed locations, says Langlois, where it continuously monitors air samples and automatically reports the presence of specific biological agents. APDS is targeted for domestic applications in which the public is at high risk of exposure to covert releases of bioagents - subway systems, transportation terminals, large office complexes, and convention centers. .... APDS provides the ability to measure up to 100 different agents and controls in a single sample,' Langlois says. 'It's being used in public buildings right now."

Appellants' claimed invention is illustrated in Appellants' original FIGS. 3, 6, 11, and 13 reproduced below and described in the portions of Appellants' original specification quoted below and identified by the page and line numbers.

"At present there are more than 30 pathogens and toxins on various agency threat lists. Public health personnel rarely see most of the pathogens so they have difficulty identifying them quickly. In addition, many pathogenic infections aren't immediately symptomatic, with delays as long as several days, limiting options to control the disease and treat the patients. The lack of a practical monitoring network capable of rapidly detecting and identifying multiple pathogens or toxins on current threat lists translates into a major deficiency in the United States ability to counter biological terrorism." (Page 11, lines 18-19 and Page 12, lines 1-6)

"There exists a critical need to develop distributed biothreat agent sensor networks that can operate in civilian applications. To operate in "Detect to Protect/Warn" type detection architectures, these platforms need to have several

key properties. They need to be capable of detecting pathogens within a 1-2 hour time window, allowing for enough time to respond to an event. They need to be extremely low cost to maintain, since continuous monitoring is essential for many applications. These platforms need to have sufficient sensitivity to cover a broad geographical area (limiting the necessary number of sensors) and have sufficient selectivity to virtually eliminate false positives." (Page 1, lines 17-19 and Page 2, lines 1-9)

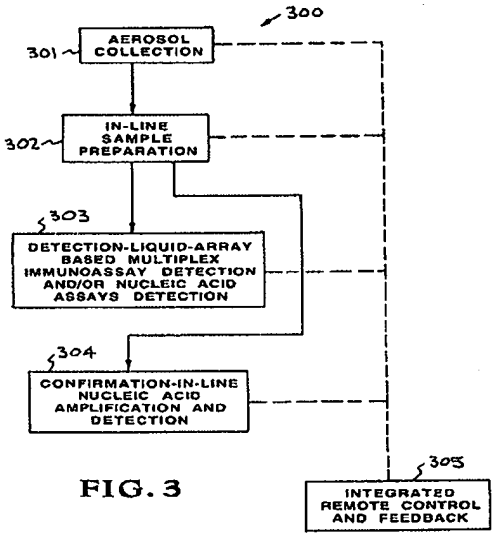


FIG. 3

"Referring now to FIG. 3 through FIG. 12 a specific embodiment of the invention designated as an AUTONOMOUS PATHOGEN DETECTION SYSTEM (APDS) is shown. The APDS is designated generally by the reference numeral 300. The APDS 300 integrates a flow cytometer and PCR detector with sample collection, sample preparation, and fluidics to provide a compact, autonomously operating instrument capable of simultaneously detecting multiple pathogens and/or toxins. The APDS 300 is designed for locations where it continuously monitors air samples and automatically reports the presence of specific biological agents. Plague and anthrax are two of the pathogens the APDS

300 identifies, along with a host of others." (Page 19, lines 20-27 and Page 20, lines 1-2)

"Particles in the air are separated by size and the particles of a size range that are likely to contain the bioagents are collected. Any bioagents in the collected particles are detected by a detector system." (Page 6, lines 7-10 & FIGS. 6, 11, and 13 below)

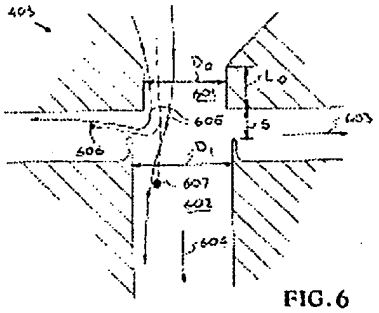
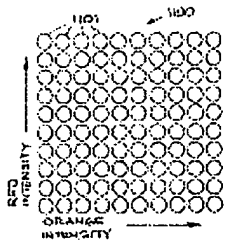


FIG. 6



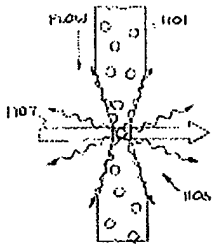


FIG. 13

"Small diameter polystyrene beads are coded with 1000s of antibodies. The sample is first exposed to the beads and the bioagent, if present, is bound to the bead. A second, fluorescently labeled antibody is then added to the sample resulting in a highly fluorescent target for flow analysis. Since the assay is performed on a microbead matrix, it is possible to measure all types of pathogens, including viruses and toxins. Each microbead is colored with a unique combination of red and orange emitting dyes. The number of agents that can be detected from a single sample is limited only by the number of colored bead sets. The system includes the following components: microbead specific reagents, incubation/mixing chambers, a microbead capture array, and an optical measurement and decoding system." (Page 41, lines 17-19 and Page 41, lines 1-8)

There is one (1) independent claim, claim 1, involved in the appeal. Appellants' independent claim involved in the appeal is "read on" Appellants' original specification.

Claim 1	Specification & Drawings
An autonomous monitoring apparatus for monitoring air for bioagents wherein the air may contain potential bioagent particles, comprising:	The present invention provides a system for monitoring air for bioagents. Particles in the air are separated by size and the particles of a size range that are likely to contain the bioagents are collected. (Page 6, lines 7-9)
a collector for gathering said air being monitored, said collector separating selected potential bioagent particles from said air;	an aerosol collector system continuously samples the air and traps particles in a swirling buffer solution. Particles of a given size distribution are selected by varying the flow rate across a virtual impactor unit. (Page 21, lines 5-8)
a wetted wall sample preparer for preparing a sample of said selected potential bioagent particles, said wetted wall sample preparer operatively connected to said collector for collecting and preparing said sample from said air gathered by said collector wherein said wetted wall sample preparer includes a wetted wall cyclone collector that concentrates said selected potential bioagent particles in a liquid and a unit for adding optically encoded microbeads imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen to said liquid and said selected potential bioagent particles; and	... the collector includes a wetted-wall cyclone collector that receives product air flow and traps and concentrates potential bioagent particles of a predetermined particle size range in a liquid. (Page 7, lines 13-15) The beads are imbedded with precise ratios of red and orange fluorescent dyes yielding an array of one hundred beads, each with a unique spectral address. Each bead 1101 is coated with capture antibodies specific for a given antigen as illustrated in FIG. 12. (Page 44, lines 11-14)
a detector for detecting said bioagents in said sample, said detector operatively connected to said wetted wall sample preparer wherein said detector utilizes said optically encoded microbeads and	A detector for detecting the bioagents in the sample is operatively connected to the sample preparation means. (Page 6, lines 18-19)

Claim 1 (Continued)	Specification & Drawings
wherein said detector includes a flow cytometer for analyzing said optically encoded microbeads that are imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen with a laser unit for individually interrogating said optically encoded microbeads and detecting said bioagents.	The APDS 300 integrates a flow cytometer and PCR detector (Page 19, line 5) Each optically encoded and fluorescently labeled microbead is individually read in a flow cytometer, and fluorescent intensities are then correlated with bioagent concentrations. (Page 19, line 5)

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The November 14, 2008 Office Action states four (4) grounds of rejection. The four grounds of rejection are summarized as follows:

Grounds of Rejection #1 – Claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Irving et al U.S. Patent No. 6,468,330 (hereinafter "Irving") in view of Casey et al U.S. Published Patent Application No. 2002/0187470 (hereinafter "Casey"). The rejection is stated in numbered paragraph 5 on pages 2-4 of the November 14, 2008 Office Action.

Grounds of Rejection #2 – Claim 19 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Irving in view of Casey and further in view of Colston, Jr. et al U.S. Published Patent Application No. 2003/0032172 (hereinafter "Colston"). The rejection is stated in numbered paragraph 16 on pages 6-7 of the November 14, 2008 Office Action.

Grounds of Rejection #3 – Claim 29 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Irving in view of Casey and further in view of Fisher et al U.S. Patent No. 6,897,031 (hereinafter "Fisher"). The rejection is stated in numbered paragraph 17 on page 7 of the November 14, 2008 Office Action.

Grounds of Rejection #4 – Claims 31 and 34 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Irving in view of Casey and further in view of Miles et al U.S. Patent No. 6,576,459 (hereinafter "Miles"). The rejection is stated on page 8 of the November 14, 2008 Office Action.

VII. ARGUMENT

Argument Relating to Grounds of Rejection #1 – The rejection in Grounds of Rejection #1 is respectfully traversed because claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40 are not obvious over the Irving reference in view of the Casey reference and claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40 are patentable.

The Irving Reference

The Irving reference is United States Patent No. 6,468,330 for a mini-cyclone biocollector and concentrator. The Irving reference is illustrated in FIGS. 1 and 2 from the Irving reference reproduce below and described in the portions of the Irving reference specification quoted below.

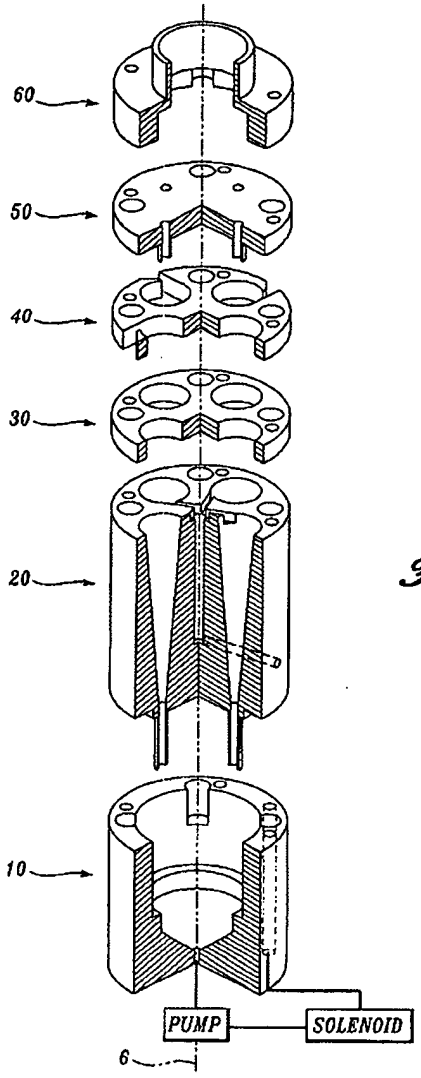


Fig. 1.

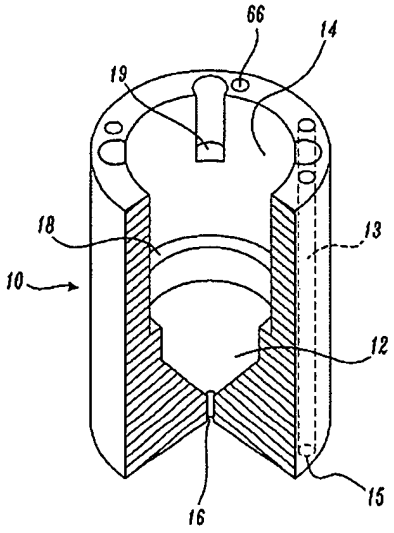


Fig. 2.

"As shown in FIGS. 1 and 2, the mini-cyclone particle separator assembly 2 includes base section 10 comprising an internal reservoir 12 and a lower vacuum chambers 14. Referring to FIGS. 1, 2 and 3B, lower vacuum chambers 14 is located toward the top of base section 10 adjacent underfluid or flow pipe outlet 28 of conical cyclone section 20 discussed below. Lower vacuum chambers 14 is connected in fluid or flow communication to four vacuum transfer channels 52 at lower openings 19. Each opening 19 is located adjacent to underfluid or flow pipes 28. Reservoir 12 stores the liquid and provides a collection location to receive liquid from underfluid or flow pipe 28. At the bottom of the base section 10, a small diameter central outlet 16 is provided to connect to the suction side of a peristaltic pump (not shown). The pump, in operation with a solenoid valve, lifts the liquid from internal reservoir 12 upwardly through a central liquid passage 24 of cyclone section 20 and into the top of the cyclone chambers 22. Base section 10 may include an internal shoulder 18 located approximately midway down the

height of interior wall of base section 10. Internal shoulder 18 provides support for three screens (not shown) that break up any foam in the liquid stream fluid or flowing out of underfluid or flow pipe 28. The control unit (not shown) can direct the liquid collected through a conduit attached to outlet 16 to a monitoring system to check for the presence of toxic microorganisms among the particles collected." (Column 6, lines 47-67 and Column 7, lines 1-7 of the Irving Reference)

The Casey Reference

The Casey reference is United States Published Patent Application No. 2002/0187470 disclosing methods for rapid detection of single nucleotide polymorphisms (SNPs) in a nucleic acid sample. The Casey reference discloses the following method:

"a method of determining a selected nucleotide polymorphism in genomic DNA treated to reduce viscosity comprising (a) performing an amplification of the genomic DNA using a first nucleic acid primer comprising a region complementary to a section of one strand of the nucleic acid that is 5' of the selected nucleotide, and a second nucleic acid primer complimentary to a section of the opposite strand of the nucleic acid downstream of the selected nucleotide, under conditions for specific amplification of the region of the selected nucleotide between the two primers, to form a PCR product; (b) contacting the PCR product with a first nucleic acid linked at its 5' end to a detectably tagged mobile solid support, wherein the first nucleic acid comprises a region complementary to a section of one strand of the PCR product that is directly 5' of and adjacent to the selected nucleotide, under hybridization conditions to form a hybridization product; (c) performing a primer extension reaction with the hybridization product and a detectably labeled, identified chain-terminating nucleotide under conditions for primer extension; (d) detecting the presence or absence of a label incorporated into the hybridization product, the presence of a label indicating the incorporation of the labeled chain-terminating nucleotide into the hybridization product, and the identity of the incorporated labeled chain-terminating nucleotide indicating the identity of the nucleotide complementary to the selected nucleotide; and (e) comparing the identity of the selected nucleotide with a non-polymorphic nucleotide, a different identity of the selected nucleotide from that of the non-polymorphic nucleotide indicating a polymorphism of that selected nucleotide."

Prima Facie Case of Obviousness Has Not Been Established

The Examiner bears the initial burden of factually supporting a prima facie conclusion of obviousness (M.P.E.P. Section 2142). Three basic criteria must be met in order for the Examiner to establish a prima facie case of obviousness.

Criterion 1 - The prior art reference (or reference when combined) must teach or suggest all the claim limitations.

Criterion 2 - There must be a reasonable expectation of success with the proposed combination.

Criterion 3 - The Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

Criterion 1 - References Do Not Teach All Claim Limitations

The criterion that prior art reference, or references when combined, must teach or suggest all the claim limitations has not been met. Appellants' invention of claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40 is an apparatus with a specific combination of structural components. The Irving and Casey references fail to show Appellants' specific combination of structural components specified in claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40. Appellants point out that the Irving and Casey references fail to teach the following claim limitations of Appellants' claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40:

Autonomous Monitoring Apparatus

The Irving and Casey references fail to teach the autonomous monitoring apparatus of Appellants' claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40. Appellants' original specification in paragraph [0004] states, "There exists a critical need to develop distributed biothreat agent sensor networks that can operate in civilian

applications. To operate in "Detect to Protect/Warn" type detection architectures, these platforms need to have several key properties. They need to be capable of detecting pathogens within a 1-2 hour time window, allowing for enough time to respond to an event. They need to be extremely low cost to maintain, since continuous monitoring is essential for many applications. These platforms need to have sufficient sensitivity to cover a broad geographical area (limiting the necessary number of sensors) and have sufficient selectivity to virtually eliminate false positives. Currently available bio-weapons detection systems are designed primarily for military use on the battlefield. These systems are often expensive to deploy and ultimately unsuited for civilian protection."

Neither the Irving reference or the Casey reference shows or teaches Appellants' "autonomous monitoring apparatus for monitoring air for bioagents wherein the air may contain potential bioagent particles" of claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40. The Irving reference does not mention "autonomous monitoring" "for monitoring air for bioagents wherein the air may contain potential bioagent particles" and the Casey reference does not even mention "monitoring" of any kind.

Collector for Gathering Air Being Monitored

Neither the Irving reference or the Casey reference shows or teaches Appellants' claim limitation, "a collector for gathering said air being monitored, said collector separating selected potential bioagent particles from said air" of Appellants' claims 1, 2, 3, and 5.

Wetted Wall Sample Preparer Operatively Connected to Said Collector

Neither the Irving reference or the Casey reference shows or teaches Appellants' claim limitation, "a wetted wall sample preparer for preparing a sample of said selected potential bioagent particles, said wetted wall sample preparer operatively connected to said collector for collecting and preparing said

sample from said air gathered by said collector wherein said wetted wall sample preparer" of Appellants' claims 1, 15, and 16.

Cyclone Collector/Unit For Adding Optically Encoded Microbeads

Neither the Irving reference or the Casey reference shows or teaches Appellants' claim limitation, "wherein said wetted wall sample preparer includes a wetted wall cyclone collector that concentrates said selected potential bioagent particles in a liquid and a unit for adding optically encoded microbeads imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen to said liquid and said selected potential bioagent particles" of Appellants' claim 1.

Detector Operatively Connected to said Wetted Wall Sample Preparer

Neither the Irving reference or the Casey reference shows or teaches Appellants' claim limitation, "a detector for detecting said bioagents in said sample, said detector operatively connected to said wetted wall sample preparer wherein said detector utilizes said optically encoded microbeads" of claims 1, 32, 35, 36, 37, 38, and 39.

Flow Cytometer & Laser Unit

Neither the Irving reference or the Casey reference shows or teaches Appellants' claim limitation, "wherein said detector includes a flow cytometer for analyzing said optically encoded microbeads that are imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen with a laser unit for individually interrogating said optically encoded microbeads and detecting said bioagents" of claim 1.

Since the limitations listed and described above are not shown by the Irving reference or the Casey reference or any combination of the Irving

reference and the Casey reference, a prima facie case of obviousness has not been established. Further, since the Irving reference and the Casey reference fail to show the claim limitations of Appellant's claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40 there can be no combination of the two references that would show Appellant's invention. There is no combination of Irving reference and the Casey reference that would produce the combination of elements of Appellant's claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40. The combination of the Irving and the Casey references in the November 14, 2008 Office Action fails to support the rejection of claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40 under 35 U.S.C. § 103(a) and the rejection should be reversed.

Appellants have identified numerous claim limitations that are not taught or suggested by the Irving reference or the Casey reference or any combination of the Irving reference and the Casey reference. If one ore more of the claim limitations are found to missing from the Irving reference and the Casey reference or any combination of the Irving reference and the Casey reference, the rejection in Grounds of Rejection #1 should be reversed.

Criterion 2 - No Reasonable Expectation of Success

The criterion that there must be a reasonable expectation of success with the proposed combination has not been met. There could be no combination of the Irving reference and the Casey reference that would provide a reasonable expectation of success or that would show Appellants' invention of claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40.

The Irving reference does not mention "autonomous monitoring" "for monitoring air for bioagents wherein the air may contain potential bioagent particles." The Casey reference does not even mention "monitoring" of any kind. There could be no combination of the two references that would have reasonable expectation of success in providing Appellant's claimed "autonomous

monitoring apparatus for monitoring air for bioagents wherein the air may contain potential bioagent particles."

As described above, both the Irving reference and the Casey reference lack numerous claim limitations of Appellants' claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40. There could be no combination of the two references that would show Appellants' invention of claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40.

Accordingly, the November 14, 2008 Office Action fails to support the rejection of claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40 under 35 U.S.C. § 103(a) and the rejection should be reversed.

Criterion 3 – No Reasons for Combining the References

The criterion that the Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007" can not be met. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

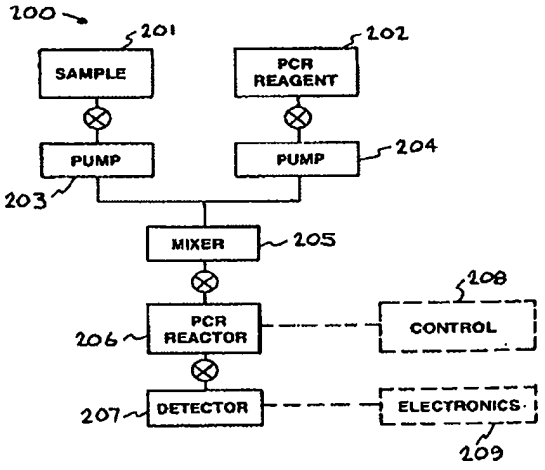
The November 14, 2008 Office Action does not identify where specific structural elements that correspond to the structural elements of Appellants' claim 1-5, 12, 15, 16, 27, 32, 33, and 35-40 are shown in the Irving reference or the Casey reference. In fact the Irving reference and the Casey reference lack the claim elements identified above in the "Criterion 1 - References Do Not Teach All Claim Limitations" section.

The rejection in the November 14, 2008 Office Action does not provide an explanation or reasons of how or why the Irving reference and the Casey reference would or could be combined. Thus, the combination of references in the November 14, 2008 Office Action fails to support a rejection of claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40 under 35 U.S.C. § 103(a) and the rejection should be reversed.

Argument Relating to Grounds of Rejection #2 – The rejection in Grounds of Rejection #2 is respectfully traversed because claim 19 is not obvious over the Irving reference in view of the Casey reference and further in view of the Colston reference and claim 19 is patentable. The Irving reference and the Casey reference are described above.

The Colston Reference

The Colston reference is United States Published Patent Application No. 2003/0032172 for a nucleic acid assay system for analyzing a sample using a reagent. The Colston reference is illustrated in FIG. 2 from the Colston reference reproduce below and described in the portions of the Colston reference specification quoted below.



"[0050] Referring now to FIG. 2, another system for performing autonomous, nucleic acid assay is illustrated. The system is generally designated by the reference numeral 200. The system 200 provides a system capable of performing, singly or in combination, sample preparation, nucleic acid amplification, and nucleic acid detection functions. The nucleic acid assay system 200 includes a number components. A sample is contained in unit 201. A PCR reagent is contained in unit 202. A pump 203 transfers the sample from unit 201 into mixer 205. A pump 204 transfers the PCR reagent from unit 202 into mixer 205." (Page 4 Right Column of the Colston Reference)

Prima Facie Case of Obviousness Has Not Been Established

The Examiner bears the initial burden of factually supporting a *prima facie* conclusion of obviousness (M.P.E.P. Section 2142). Three basic criteria must be met in order for the Examiner to establish a *prima facie* case of obviousness.

Criterion 1 - The prior art reference (or reference when combined) must teach or suggest all the claim limitations.

Criterion 2 - There must be a reasonable expectation of success with the proposed combination.

Criterion 3 - The Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

Criterion 1 - References Do Not Teach All Claim Limitations

The criterion that prior art reference, or references when combined, must teach or suggest all the claim limitations has not been met. Appellants' invention of claim 19 is an apparatus with a specific combination of structural components. The Irving, Casey, and Colston references fail to show Appellants' specific combination of structural components specified in claim 19.

Irving and Casey References

As explained above in connection with Appellants' Argument Relating to Grounds of Rejection #1, the Irving reference and the Casey reference fail to teach the claim limitations of Parent Claim 1 of Appellants' Claim 19: "the autonomous monitoring apparatus," or "a collector for gathering said air being monitored, said collector separating selected potential bioagent particles from said air," or "a wetted wall sample preparer for preparing a sample of said selected potential bioagent particles, said wetted wall sample preparer

operatively connected to said collector for collecting and preparing said sample from said air gathered by said collector wherein said wetted wall sample preparer," or "wherein said wetted wall sample preparer includes a wetted wall cyclone collector that concentrates said selected potential bioagent particles in a liquid and a unit for adding optically encoded microbeads imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen to said liquid and said selected potential bioagent particles," or "a detector for detecting said bioagents in said sample, said detector operatively connected to said wetted wall sample preparer wherein said detector utilizes said optically encoded microbeads," or "wherein said detector includes a flow cytometer for analyzing said optically encoded microbeads that are imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen with a laser unit for individually interrogating said optically encoded microbeads and detecting said bioagents." The Irving reference and the Casey reference also fail to teach the claim limitation of Appellants' Claim 19: "a super serpentine reactor."

The Colston Reference

The Colston reference fails to teach the claim limitations of Parent Claim 1 of Appellants' Claim 19: "the autonomous monitoring apparatus," or "a collector for gathering said air being monitored, said collector separating selected potential bioagent particles from said air," or "a wetted wall sample preparer for preparing a sample of said selected potential bioagent particles, said wetted wall sample preparer operatively connected to said collector for collecting and preparing said sample from said air gathered by said collector wherein said wetted wall sample preparer," or "wherein said wetted wall sample preparer

includes a wetted wall cyclone collector that concentrates said selected potential bioagent particles in a liquid and a unit for adding optically encoded microbeads imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen to said liquid and said selected potential bioagent particles," or "a detector for detecting said bioagents in said sample, said detector operatively connected to said wetted wall sample preparer wherein said detector utilizes said optically encoded microbeads," or "wherein said detector includes a flow cytometer for analyzing said optically encoded microbeads that are imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen with a laser unit for individually interrogating said optically encoded microbeads and detecting said bioagents."

Irving, Casey, and Colston References Lack Claim Limitations

Appellants have identified numerous claim limitations that are not taught or suggested by the Irving reference or the Casey reference or the Colston reference or any combination of the Irving reference and the Casey reference and the Colston reference. If one or more of the claim limitations are found to missing from the Irving reference and the Casey reference and the Colston reference or any combination of the Irving reference and the Casey reference and the Colston reference, the rejection in Grounds of Rejection #2 should be reversed.

Criterion 2 - No Reasonable Expectation of Success

The criterion that there must be a reasonable expectation of success with the proposed combination has not been met. There could be no combination of the Irving reference and the Casey reference and the Colston reference that

would provide a reasonable expectation of success or that would show Appellants' invention of claim 19.

As explained above in connection with Appellants' Argument Relating to Grounds of Rejection #1, the Irving and Casey references do not mention "autonomous monitoring" "for monitoring air for bioagents wherein the air may contain potential bioagent particles." The Colston reference does not even mention "monitoring" of any kind. There could be no combination of the three references that would have reasonable expectation of success in providing Appellant's claimed "autonomous monitoring apparatus for monitoring air for bioagents wherein the air may contain potential bioagent particles." The Irving reference and the Casey reference and the Colston reference lack numerous claim limitations of Appellants' claim 19. There could be no combination of the three references that would show Appellants' invention of claim 19. Accordingly, the November 14, 2008 Office Action fails to support the rejection of claim 19 under 35 U.S.C. § 103(a) and the rejection should be reversed.

Criterion 3 – No Reasons for Combining the References

The criterion that the Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007" can not be met. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

The November 14, 2008 Office Action does not identify where specific structural elements that correspond to the structural elements of Appellants' claim 19 are shown in the Irving reference or the Casey reference or the Colston reference. The rejection in the November 14, 2008 Office Action does not provide an explanation or reasons of how or why the Irving reference and the Casey reference and the Colston reference would or could be combined. Thus, the

combination of references in the November 14, 2008 Office Action fails to support a rejection of claim 19 under 35 U.S.C. § 103(a) and the rejection should be reversed.

Argument Relating to Grounds of Rejection #3 – The rejection in Grounds of Rejection #3 is respectfully traversed because claim 29 is not obvious over the Irving reference in view of the Casey reference and further in view of the Fisher reference and claim 29 is patentable. The Irving reference and the Casey reference are described above.

The Fisher Reference

The Fisher reference is United States Application No. 6,897,031 for detecting alterations in exocytosis in a cell or a cell population and screening for agents capable of modulating exocytosis through the use of multiparameter assays and a fluorescence-activated cell sorter (FACS) machine. The Fisher reference is described in the abstract of the Fisher reference quoted below.

> "Described is a method for screening for alterations in exocytosis of a population of cells. The cells are sorted by a FACS machine by assaying for alterations in at least three of the properties selected from the group consisting of light scattering, fluorescent dye uptake, fluorescent dye release, annexin granule binding, surface granule enzyme activity, and the quantity of granule specific proteins. Methods for screening for bioactive agents capable of modulating exocytosis in a cell are also described. The methods provide for reduced background and increased specificity without increasing the time or steps involved in assaying for exocytosis." (Abstract of the Fisher Reference)

Prima Facie Case of Obviousness Has Not Been Established

The Examiner bears the initial burden of factually supporting a *prima facie* conclusion of obviousness (M.P.E.P. Section 2142). Three basic criteria must be met in order for the Examiner to establish a *prima facie* case of obviousness.

Criterion 1 - The prior art reference (or reference when combined) must teach or suggest all the claim limitations.

Criterion 2 - There must be a reasonable expectation of success with the proposed combination.

Criterion 3 - The Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

Criterion 1 - References Do Not Teach All Claim Limitations

The criterion that prior art reference, or references when combined, must teach or suggest all the claim limitations has not been met. Appellants' invention of claim 29 is an apparatus with a specific combination of structural components. The Irving, Casey, and Fisher references fail to show Appellants' specific combination of structural components specified in claim 29. Appellants point out that the Irving, Casey, and Fisher references fail to teach the following claim limitations of Appellants' claim 29:

Irving and Casey References

As explained above in connection with Appellants' Argument Relating to Grounds of Rejection #1, the Irving reference and the Casey reference fail to teach the claim limitations of Parent Claim 1 of Appellants' Claim 29: "the autonomous monitoring apparatus," or "a collector for gathering said air being monitored, said collector separating selected potential bioagent particles from said air," or "a wetted wall sample preparer for preparing a sample of said selected potential bioagent particles, said wetted wall sample preparer operatively connected to said collector for collecting and preparing said sample from said air gathered by said collector wherein said wetted wall sample

preparer," or "wherein said wetted wall sample preparer includes a wetted wall cyclone collector that concentrates said selected potential bioagent particles in a liquid and a unit for adding optically encoded microbeads imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen to said liquid and said selected potential bioagent particles," or "a detector for detecting said bioagents in said sample, said detector operatively connected to said wetted wall sample preparer wherein said detector utilizes said optically encoded microbeads," or "wherein said detector includes a flow cytometer for analyzing said optically encoded microbeads that are imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen with a laser unit for individually interrogating said optically encoded microbeads and detecting said bioagents." The Irving reference and the Casey reference also fail to teach the claim limitation of Appellants' Claim 29: "wherein said flow cytometer for analyzing said optically encoded microbeads with said laser unit includes a red laser that classifies said microbeads and a green laser that quantifies said microbeads."

The Fisher Reference

The Fisher reference fails to teach the claim limitations of Parent Claim 1 of Appellants' Claim 29: "the autonomous monitoring apparatus," or "a collector for gathering said air being monitored, said collector separating selected potential bioagent particles from said air," or "a wetted wall sample preparer for preparing a sample of said selected potential bioagent particles, said wetted wall sample preparer operatively connected to said collector for collecting and preparing said sample from said air gathered by said collector wherein said wetted wall sample preparer," or "wherein said wetted wall sample preparer

includes a wetted wall cyclone collector that concentrates said selected potential bioagent particles in a liquid and a unit for adding optically encoded microbeads imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen to said liquid and said selected potential bioagent particles," or "a detector for detecting said bioagents in said sample, said detector operatively connected to said wetted wall sample preparer wherein said detector utilizes said optically encoded microbeads," or "wherein said detector includes a flow cytometer for analyzing said optically encoded microbeads that are imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen with a laser unit for individually interrogating said optically encoded microbeads and detecting said bioagents."

Irving, Casey, and Fisher References Lack Claim Limitations

Appellants have identified numerous claim limitations that are not taught or suggested by the Irving reference or the Casey reference or the Fisher reference or any combination of the Irving reference and the Casey reference and the Fisher reference. If one ore more of the claim limitations are found to missing from the Irving reference and the Casey reference and the Fisher reference or any combination of the Irving reference and the Casey reference and the Fisher reference, the rejection in Grounds of Rejection #3 should be reversed.

Criterion 2 - No Reasonable Expectation of Success

The criterion that there must be a reasonable expectation of success with the proposed combination has not been met. There could be no combination of the Irving reference and the Casey reference and the Fisher reference that would

provide a reasonable expectation of success or that would show Appellants' invention of claim 29.

As explained above in connection with Appellants' Argument Relating to Grounds of Rejection #1, the Irving and Casey references do not mention "autonomous monitoring" "for monitoring air for bioagents wherein the air may contain potential bioagent particles." The Fisher reference does not even mention "monitoring" of any kind. There could be no combination of the three references that would have reasonable expectation of success in providing Appellant's claimed "autonomous monitoring apparatus for monitoring air for bioagents wherein the air may contain potential bioagent particles." The Irving reference and the Casey reference and the Fisher reference lack numerous claim limitations of Appellants' claim 29. There could be no combination of the three references that would show Appellants' invention of claim 29. Accordingly, the November 14, 2008 Office Action fails to support the rejection of claim 29 under 35 U.S.C. § 103(a) and the rejection should be reversed.

Criterion 3 – No Reasons for Combining the References

The criterion that the Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007" can not be met. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

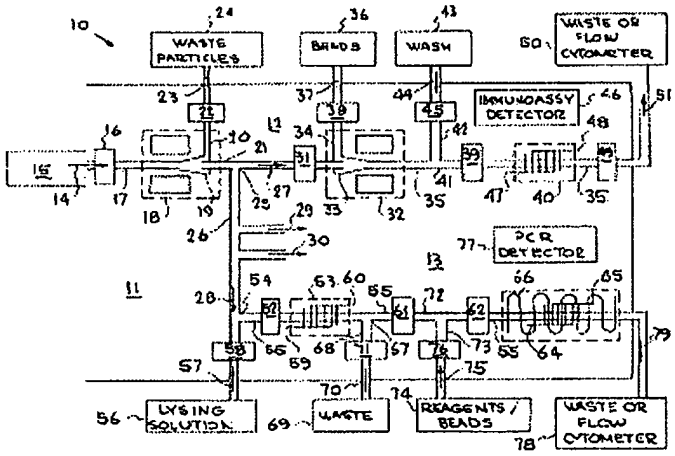
The November 14, 2008 Office Action does not identify where specific structural elements that correspond to the structural elements of Appellants' claim 29 are shown in the Irving reference or the Casey reference or the Fisher reference. The rejection in the November 14, 2008 Office Action does not provide an explanation or reasons of how or why the Irving reference and the Casey reference and the Fisher reference would or could be combined. Thus, the

combination of references in the November 14, 2008 Office Action fails to support a rejection of claim 29 under 35 U.S.C. § 103(a) and the rejection should be reversed.

Argument Relating to Grounds of Rejection #4 – The rejection in Grounds of Rejection #4 is respectfully traversed because claims 31 and 34 are not obvious over the Irving reference in view of the Casey reference and further in view of the Miles reference and claims 31 and 34 is patentable. The Irving reference and the Casey reference are described above.

The Miles Reference

The Miles reference is United States Patent No. 6,576,459 for a sample preparation and detection device for infectious agents illustrated in the figure and portion of specification of the patent reproduced below.



"The sample preparation and detection device comprises a system or device generally indication at 10 located on a single compact, field-portable microchip 11 and includes an immunoassay section 12 and a PCR assay section 13. Sample containing pathogenic particles indicated by arrow 14 is moved from a collector or other source 15 by an MHD pump 16 through a microchannel 17 into an ultrasonic fractionation or filtering assembly generally indicated at 18 and which is sensitive to density and size differences between particles. Microchannel 17 terminates in a separator 19 with microchannels 20 and 21 extending from separator 19. Microchannel 20 is directed through a MHD

pump 22 and carries large particles and dense particles indicated by arrow 23, which are transferred to waste as indicated at 24. Microchannel 21 includes a function 25 from which extends a microchannel 26, with microchannel 21 supplying sample to immunoassay section 12 as indicated by arrow 27 and microchannel 26 supplying sample to PCR assay section 13 for DNA analysis, as indicated by arrow 28."

Prima Facie Case of Obviousness Has Not Been Established

The Examiner bears the initial burden of factually supporting a *prima facie* conclusion of obviousness (M.P.E.P. Section 2142). Three basic criteria must be met in order for the Examiner to establish a *prima facie* case of obviousness.

Criterion 1 - The prior art reference (or reference when combined) must teach or suggest all the claim limitations.

Criterion 2 - There must be a reasonable expectation of success with the proposed combination.

Criterion 3 - The Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

Criterion 1 - References Do Not Teach All Claim Limitations

The criterion that prior art reference, or references when combined, must teach or suggest all the claim limitations has not been met. Appellants' invention of claims 31 and 34 is an apparatus with a specific combination of structural components. The Irving, Casey, and Miles references fail to show Appellants' specific combination of structural components specified in claims 31 and 34. Appellants point out that the Irving, Casey, and Miles references fail to teach the following claim limitations of Appellants' claims 31 and 34:

Irving and Casey References

As explained above in connection with Appellants' Argument Relating to Grounds of Rejection #1, the Irving reference and the Casey reference fail to teach the claim limitations of Parent Claim 1 of Appellants' Claims 31 and 34: "the autonomous monitoring apparatus," or "a collector for gathering said air being monitored, said collector separating selected potential bioagent particles from said air," or "a wetted wall sample preparer for preparing a sample of said selected potential bioagent particles, said wetted wall sample preparer operatively connected to said collector for collecting and preparing said sample from said air gathered by said collector wherein said wetted wall sample preparer," or "wherein said wetted wall sample preparer includes a wetted wall cyclone collector that concentrates said selected potential bioagent particles in a liquid and a unit for adding optically encoded microbeads imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen to said liquid and said selected potential bioagent particles," or "a detector for detecting said bioagents in said sample, said detector operatively connected to said wetted wall sample preparer wherein said detector utilizes said optically encoded microbeads," or "wherein said detector includes a flow cytometer for analyzing said optically encoded microbeads that are imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen with a laser unit for individually interrogating said optically encoded microbeads and detecting said bioagents."

The Irving reference and the Casey reference also fail to teach the claim limitation of Appellants' Claim 31: "wherein said detector includes a multiplex PCR detector." In addition, the Irving reference and the Casey reference also fail

to teach the claim limitation of Appellants' Claim 34: "wherein said confirmation means is a multiplex immunoassay detector."

The Miles Reference

The Miles reference fails to teach the claim limitations of Parent Claim 1 of Appellants' Claims 31 and 34: "the autonomous monitoring apparatus," or "a collector for gathering said air being monitored, said collector separating selected potential bioagent particles from said air," or "a wetted wall sample preparer for preparing a sample of said selected potential bioagent particles, said wetted wall sample preparer operatively connected to said collector for collecting and preparing said sample from said air gathered by said collector wherein said wetted wall sample preparer," or "wherein said wetted wall sample preparer includes a wetted wall cyclone collector that concentrates said selected potential bioagent particles in a liquid and a unit for adding optically encoded microbeads imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen to said liquid and said selected potential bioagent particles," or "a detector for detecting said bioagents in said sample, said detector operatively connected to said wetted wall sample preparer wherein said detector utilizes said optically encoded microbeads," or "wherein said detector includes a flow cytometer for analyzing said optically encoded microbeads that are imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen with a laser unit for individually interrogating said optically encoded microbeads and detecting said bioagents."

Irving, Casey, and Miles References Lack Claim Limitations

Appellants have identified numerous claim limitations that are not taught or suggested by the Irving reference or the Casey reference or the Miles reference or any combination of the Irving reference and the Casey reference and the Miles reference. If one ore more of the claim limitations are found to missing from the Irving reference and the Casey reference and the Miles reference or any combination of the Irving reference and the Casey reference and the Miles reference, the rejection in Grounds of Rejection #4 should be reversed.

Criterion 2 - No Reasonable Expectation of Success

The criterion that there must be a reasonable expectation of success with the proposed combination has not been met. There could be no combination of the Irving reference and the Casey reference and the Miles reference that would provide a reasonable expectation of success or that would show Appellants' invention of claims 31 and 34.

As explained above in connection with Appellants' Argument Relating to Grounds of Rejection #1, the Irving and Casey references do not mention "autonomous monitoring" "for monitoring air for bioagents wherein the air may contain potential bioagent particles." The Miles reference does not even mention "monitoring" of any kind. There could be no combination of the three references that would have reasonable expectation of success in providing Appellant's claimed "autonomous monitoring apparatus for monitoring air for bioagents wherein the air may contain potential bioagent particles." The Irving reference and the Casey reference and the Miles reference lack numerous claim limitations of Appellants' claims 31 and 34. There could be no combination of the three references that would show Appellants' invention of claims 31 and 34. Accordingly, the November 14, 2008 Office Action fails to support the rejection of claims 31 and 34 under 35 U.S.C. § 103(a) and the rejection should be reversed.

Criterion 3 – No Reasons for Combining the References

The criterion that the Examiner must follow the "Examination Guidelines for Determining Obviousness in Light of the Supreme Court's KSR v. Teleflex Decision" published October 10, 2007" can not be met. These guidelines include the requirement that the Examiner provide reasons for combining the references to produce the proposed combination.

The November 14, 2008 Office Action does not identify where specific structural elements that correspond to the structural elements of Appellants' claims 31 and 34 are shown in the Irving reference or the Casey reference or the Miles reference. The rejection in the November 14, 2008 Office Action does not provide an explanation or reasons of how or why the Irving reference and the Casey reference and the Miles reference would or could be combined. Thus, the combination of references in the November 14, 2008 Office Action fails to support a rejection of claims 31 and 34 under 35 U.S.C. § 103(a) and the rejection should be reversed.

Secondary Considerations - Claim 1-5, 12, 15-16, 19, 27, 29, and 31-40

Appellants believe the November 14, 2008 Office Action fails to establish a *prima facie* case of obviousness; however, even if a *prima facie* case of obviousness was established Appellants submit a showing of secondary considerations that supports "unobviousness" and patentability of Appellants' invention. The invention of Appellants' claims 1-5, 12, 15-16, 19, 27, 29, and 31-40 provides unexpected results, has been licensed, has obtained commercial success, has obtained recognition by peers, has obtained praise by others, and fulfills an important and long felt need. These secondary considerations support "unobviousness" and patentability of Appellants' invention defined by claims 1-5, 12, 15-16, 19, 27, 29, and 31-40 on appeal.

Appellants' Invention Provides Unexpected Results

Appellants' invention defined by claims 1-5, 12, 15-16, 19, 27, 29, and 31-40 on appeal produces unexpected results compared to the prior art references in the November 14, 2008 Office Action. None of the prior art references teach the "Autonomous Pathogen Detection System" apparatus of Appellants' claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40. The prior art references in the November 14, 2008 Office Action fail to teach the concept of "autonomous monitoring" "for monitoring air for bioagents wherein the air may contain potential bioagent particles" as claimed in Appellants' claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40. Accordingly, Appellants' invention of claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40 that does teach the "Autonomous Pathogen Detection System" apparatus produces unexpected results.

None of the prior art references in the November 14, 2008 Office Action recognize the problem solved by the invention of Appellants' claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40. Appellants' original specification in paragraph [0004] states, "There exists a critical need to develop distributed biothreat agent sensor networks that can operate in civilian applications. To operate in "Detect to Protect/Warn" type detection architectures, these platforms need to have several key properties. They need to be capable of detecting pathogens within a 1-2 hour time window, allowing for enough time to respond to an event. They need to be extremely low cost to maintain, since continuous monitoring is essential for many applications. These platforms need to have sufficient sensitivity to cover a broad geographical area (limiting the necessary number of sensors) and have sufficient selectivity to virtually eliminate false positives. Currently available bio-weapons detection systems are designed primarily for military use on the battlefield. These systems are often expensive to deploy and ultimately unsuited for civilian protection." Accordingly, Appellants' invention of claims 1-5, 12, 15,

16, 27, 32, 33, and 35-40 that recognizes and solves the problem produces unexpected results.

Appellants' Invention Has Been Licensed

Appellants' Autonomous Pathogen Detection System (APDS) invention defined by claims 1-5, 12, 15-16, 19, 27, 29, and 31-40 on appeal has been licensed. The August 29, 2008 article "Bioterrorism Detection System (APDS)," in the publication *Homeland Security*, states: "The APDS technology has been licensed and is currently undergoing commercialization." a copy of the August 29, 2008 article "Bioterrorism Detection System (APDS)," in the publication *Homeland Security*, is included in the Evidence Appendix IX.

Appellants' Invention Has Obtained Commercial Success

Appellants' Autonomous Pathogen Detection System (APDS) invention defined by claims 1-5, 12, 15-16, 19, 27, 29, and 31-40 on appeal has obtained commercial success. As stated in, the August 29, 2008 article "Bioterrorism Detection System (APDS)," a copy of which is included in the Evidence Appendix IX, "Shaped like a mailbox on wheels, it's been called a bioterrorism "smoke detector." It can be found in transportation hubs such as airports and subways. Formally known as the Autonomous Pathogen Detection System, or APDS, this latest tool in the war on bioterrorism was developed at Lawrence Livermore National Laboratory to continuously sniff the air for airborne pathogens and toxins such as anthrax or plague. The APDS technology has been licensed and is currently undergoing commercialization. In September 2003, APDS passed a series of pathogen exposure tests at a high-containment laboratory at the Dugway Proving Ground in Utah. In these trials, the system clearly demonstrated that it could detect real pathogens and confirm the identifications with a fully automated second assay method. APDS units were also deployed at the Albuquerque Airport in New Mexico and at a Washington,

DC, Metro station, where they provided continuous monitoring for up to seven days, unattended."

Invention Has Obtained Recognition by Peers & Praise by Others

Appellants' Autonomous Pathogen Detection System (APDS) invention defined by claims 1-5, 12, 15-16, 19, 27, 29, and 31-40 on appeal has obtained recognition by peers and praise by others. The article "Detecting Bioaerosols When Time is of the Essence" in the October 2004 issue of *Science & Technology Review*, states:

> "ABOUT seven years ago, Livermore researchers received seed funding from the Laboratory Directed Research and Development Program to develop an instrument that counters bioterrorism by providing a rapid early warning system for pathogens, such as anthrax. (See *S&TR*, January/February 2002, Rapid Field Detection of Biological Agents.) That instrument, the Autonomous Pathogen Detection System (APDS), is now ready for deployment to better protect the public from a bioaerosol attack, and the development team has been honored with a 2004 R&D 100 Award."

A copy of the article "Detecting Bioaerosols When Time is of the Essence" in the October 2004 issue of *Science & Technology Review*, is included in the Evidence Appendix IX.

Appellants' Invention Fulfills An Important and Long Felt Need

Appellants' Autonomous Pathogen Detection System (APDS) invention defined by claims 1-5, 12, 15-16, 19, 27, 29, and 31-40 on appeal fulfills an important and long felt need. Appellants' original specification in paragraph [0004] states, "There exists a critical need to develop distributed biothreat agent sensor networks that can operate in civilian applications. To operate in "Detect to Protect/Warn" type detection architectures, these platforms need to have several key properties. They need to be capable of detecting pathogens within a 1-2 hour time window, allowing for enough time to respond to an event. They need to be

extremely low cost to maintain, since continuous monitoring is essential for many applications. These platforms need to have sufficient sensitivity to cover a broad geographical area (limiting the necessary number of sensors) and have sufficient selectivity to virtually eliminate false positives. Currently available bio-weapons detection systems are designed primarily for military use on the battlefield. These systems are often expensive to deploy and ultimately unsuited for civilian protection."

The article included in the Evidence Appendix IX, "Detecting Bioaerosols When Time is of the Essence" in the October 2004 issue of *Science & Technology Review*, states:

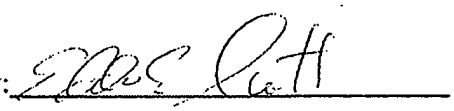
> In September 2003, APDS passed a series of pathogen exposure tests at a high-containment laboratory at the Dugway Proving Ground in Utah. In these trials, the system clearly demonstrated that it could detect real pathogens and confirm the identifications with a fully automated second assay method. APDS units were also deployed at the Albuquerque Airport in New Mexico and at a Washington, DC, Metro station, where they provided continuous monitoring for up to seven days, unattended. The system can be adapted for situations where environmental or clinical pathogens require monitoring. For example, APDS could test for mold or fungal spores in buildings or for the airborne spread of contagious materials in hospitals. It also could identify disease outbreaks in livestock transport centers or feedlots. "Basically, there are no fully integrated systems with the capabilities of APDS commercially available in the civilian or military market," notes Langlois. "The system offers ongoing environmental monitoring and rapid detection of harmful pathogens, allowing emergency workers to respond immediately to decontaminate areas and, most importantly, save lives."

Accordingly, Appellants' invention of claims 1-5, 12, 15, 16, 27, 32, 33, and 35-40 fulfills an important and long felt need.

SUMMARY

The present invention provides an autonomous monitoring apparatus for monitoring air for bioagents wherein the air may contain potential bioagent particles. One embodiment of Appellants' claimed invention is the Autonomous Pathogen Detection System (APDS) described in paragraph [0006] Appellants' original specification. There could be no combination of the references that would support a 35 U. S. C §103(a) rejection of Appellants' claims 1-5, 12, 15-16, 19, 27, 29, and 31-40. Secondary considerations that Appellants' invention provides unexpected results, has been licensed, has obtained commercial success, has obtained recognition by peers, has obtained praise by others, and fulfills an important and long felt need support "unobviousness" and patentability of Appellants' invention. The rejection of Appellants' claims 1-5, 12, 15-16, 19, 27, 29, and 31-40 on appeal should be reversed. It is respectfully requested that claims 1-5, 12, 15-16, 19, 27, 29, and 31-40 on appeal be allowed.

Respectfully submitted,

By: 

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Date: November 24, 2008

VIII. CLAIMS APPENDIX

1. An autonomous monitoring apparatus for monitoring air for bioagents wherein the air may contain potential bioagent particles, comprising:

a collector for gathering said air being monitored, said collector separating selected potential bioagent particles from said air;

a wetted wall sample preparer for preparing a sample of said selected potential bioagent particles, said wetted wall sample preparer operatively connected to said collector for collecting and preparing said sample from said air gathered by said collector wherein said wetted wall sample preparer includes a wetted wall cyclone collector that concentrates said selected potential bioagent particles in a liquid and a unit for adding optically encoded microbeads imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen to said liquid and said selected potential bioagent particles; and

a detector for detecting said bioagents in said sample, said detector operatively connected to said wetted wall sample preparer wherein said detector utilizes said optically encoded microbeads and

wherein said detector includes a flow cytometer for analyzing said optically encoded microbeads that are imbedded with precise ratios of red and orange fluorescent dyes yielding an array of beads having a unique spectral address and each bead coated with capture antibodies specific for a given antigen with a laser unit for individually interrogating said optically encoded microbeads and detecting said bioagents.

2. The apparatus of claim 1 wherein said collector is an aerosol collector.

3. The apparatus of claim 1 wherein said air includes other particles in addition to said potential bioagent particles and wherein said collector includes a

separator for separating said potential bioagent particles from said other particles.

4. The apparatus of claim 3 wherein said potential bioagent particles are of a predetermined size range and said separator separates said potential bioagent particles are of a predetermined size range from said other particles.

5. The apparatus of claim 4 wherein said collector is an aerosol collector that collects air and includes means for separating said air into a bypass air flow that does not contain said potential bioagent particles of a predetermined particle size range and a product air flow that contains said potential bioagent particles of a predetermined particle size range.

12. The apparatus of claim 1 wherein said potential bioagent particles contain spores and including means for lysis of said spores.

15. The apparatus of claim 1 wherein said wetted wall sample preparer includes a sequential injection analysis system.

16. The apparatus of claim 1 wherein said wetted wall sample preparer includes a flow injection analysis system.

19. The apparatus of claim 1 wherein said wetted wall sample preparer includes a super serpentine reactor.

27. The apparatus of claim 1 wherein said optically encoded microbeads are polystyrene beads.

29. The apparatus of claim 1 wherein said flow cytometer for analyzing said optically encoded microbeads with said laser unit includes a red laser that classifies said microbeads and a green laser that quantifies said microbeads.

31. The apparatus of claim 1 wherein said detector includes a liquid-array based multiplex immunoassay detector.

32. The apparatus of claim 1 wherein said detector includes a multiplex PCR detector.

33. The apparatus of claim 1 including confirmation means for confirming said bioagents in said sample.

34. The apparatus of claim 33 wherein said confirmation means is a multiplex immunoassay detector.

35. The apparatus of claim 33 wherein said confirmation means is a multiplex PCR detector.

36. The apparatus of claim 33 wherein said confirmation means is a real time PCR detector.

37. The apparatus of claim 33 wherein said confirmation means includes means for performing PCR amplification.

38. The apparatus of claim 33 wherein said confirmation means includes means for injecting/aspirating a sample, means for adding PCR reagent, means for mixing sample and reagent, means for transport to PCR reactor, means for performing PCR amplification, means for transport of amplified sample from PCR reactor, and means for detection of PCR amplicon.

39. The apparatus of claim 33 wherein said confirmation means includes means for injecting/aspirating a sample, means for adding PCR reagent, means for mixing sample and reagent, means for transport to PCR reactor, means for performing PCR amplification, means for transport of amplified sample from PCR reactor, means for detection of PCR amplicon, and means for decontamination and conditioning of all exposed conduits.

40. The apparatus of claim 1 wherein said sample preparation means includes optically encoded microbeads and bead suspension/mixer means for suspending said microbeads for a predetermined time period.

IX. EVIDENCE APPENDIX

Publication #1 - "Bioterrorism Detection System (APDS)," *Homeland Security,* August 29, 2008.

Publication #2 - "Detecting Bioaerosols When Time is of the Essence," *Science & Technology Review,* October 2004.

X. RELATED PROCEEDINGS APPENDIX

There are no entries in the Related Proceedings Appendix.

Bioterrorism Detection Systems http://www.globalsecurity.org/security/systems/apds.htm August 29, 2008

Autonomous Pathogen Detection System (APDS)

Shaped like a mailbox on wheels, it's been called a bioterrorism "smoke detector." It can be found in transportation hubs such as airports and subways. Formally known as the Autonomous Pathogen Detection System, or APDS, this latest tool in the war on bioterrorism was developed at Lawrence Livermore National Laboratory to continuously sniff the air for airborne pathogens and toxins such as anthrax or plague.

The APDS is the modern day equivalent of the canaries miners took underground with them to test for deadly carbon dioxide gas. But this canary can test for numerous bacteria, viruses, and toxins simultaneously, report results every hour, and confirm positive samples and guard against false positive results by using two different tests. The fully automated system collects and prepares air samples around the clock, does the analysis, and interprets the results. It requires no servicing or human intervention for an entire week.

Unlike its feathered counterpart, when an APDS unit encounters something deadly in the air, that's when it begins singing, quietly. The APDS unit transmits a silent alert and sends detailed data to public health authorities, who can order evacuation and begin treatment of anyone exposed to toxic or biological agents. It is the latest in a series of biodefense detectors developed at DOE/NNSA national laboratories.

The manual predecessor to APDS, called BASIS (for Biological Aerosol Sentry and Information System), was developed jointly by Los Alamos and Lawrence Livermore national laboratories. That system was modified to become BioWatch, the Department of Homeland Security's biological urban monitoring program. A related laboratory instrument, the Handheld Advanced Nucleic Acid Analyzer (HANAA), was first tested successfully at LLNL in September 1997.

Successful partnering with private industry has been a key factor in the rapid advancement and deployment of biodefense instruments such as these. The APDS technology has been licensed and is currently undergoing commercialization.

One of the methods a terrorist might use to disperse a biowarfare agent is through an aerosol attack. In fact, the anthrax mail room release in 2001 and the ricin release in 2004 involved relatively small amounts of deadly material. Countering such threats in an effective manner requires an automated system that continuously monitors the air, quickly analyzes samples, and identifies a wide range of agents without false positives.

APDS is designed to meet that need. It monitors the air for the three types of biological threat agents: bacteria, viruses, and toxins. Because it operates continuously, the system can detect low concentrations of bioagents that might go undetected by a system that is triggered only when the overall number of particles in the air is high. APDS collects aerosol samples, prepares them for analysis, and tests for multiple biological agents simultaneously. This automation reduces the cost and staffing that would be required to manually analyze samples.

The current system is configured to test simultaneously for 11 agents and can be expanded to 100 agents without a change in instrumentation. Given the number of pathogens potentially available to terrorists, the ability to detect and analyze large numbers is critical. APDS also identifies particles within 1 hour—faster than comparable systems, which can take 4 to 20 hours. Having results promptly is crucial for emergency-response efforts, as is being certain that the results are real

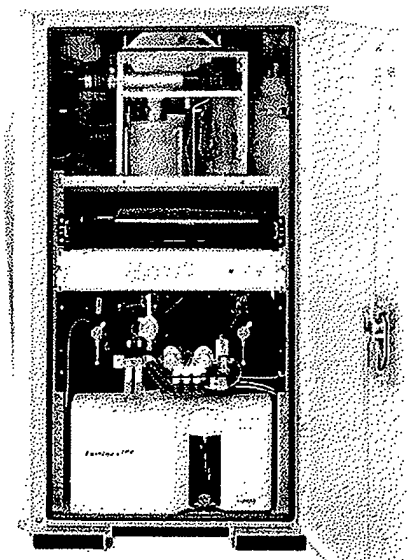
In September 2003, APDS passed a series of pathogen exposure tests at a high-containment laboratory at the Dugway Proving Ground in Utah. In these trials, the system clearly demonstrated that it could detect real pathogens and confirm the identifications with a fully automated second assay method. APDS units were also deployed at the Albuquerque Airport in New Mexico and at a Washington, DC, Metro station, where they provided continuous monitoring for up to seven days, unattended.

The system can be adapted for situations where environmental or clinical pathogens require monitoring. For example, APDS could test for mold or fungal spores in buildings or for the airborne spread of contagious materials in hospitals. It also could identify disease outbreaks in livestock transport centers or feedlots.

Detecting Bioaerosols
When Time Is of the Essence

About seven years ago, Livermore researchers received seed funding from the Laboratory Directed Research and Development Program to develop an instrument that counters bioterrorism by providing a rapid early warning system for pathogens, such as anthrax. (See *S&TR*, January/February 2002, pp. 24–26.) That instrument, the Autonomous Pathogen Detection System (APDS), is now ready for deployment to better protect the public from a bioaerosol attack, and the development team has been honored with a 2004 R&D 100 Award.

The lectern-size APDS can be placed in airports, office buildings, performing arts centers, mass transit systems, sporting arenas—anywhere an attack might be launched. APDS was designed to get results fast and get them right, without false positives. Biological scientist Richard Langlois, who spearheaded the APDS development effort, explains, "The system provides results on the spot. Faster results allow a faster emergency response, which in the end means saving lives."



The Autonomous Pathogen Detection System (APDS) monitors the air continuously for biological threat agents and uses two identification technologies to reduce the probability of false alarms. It can measure up to 100 different agents per sample and reports identified agents within an hour.

Responding Rapidly, Reliably

One of the methods a terrorist might use to disperse a biowarfare agent is through an aerosol attack. In fact, the anthrax mail room release in 2001 and the ricin release in 2004 involved relatively small amounts of deadly material. Countering such threats in an effective manner requires an automated system that continuously monitors the air, quickly analyzes samples, and identifies a wide range of agents without false positives.

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The current system is configured to test simultaneously for 11 agents and can be expanded to 100 agents without a change in instrumentation. "Given the number of pathogens potentially available to terrorists," says Langlois, "the ability to detect and analyze large numbers is critical." APDS also identifies particles within 1 hour—faster than comparable systems, which can take 4 to 20 hours. Having results promptly is crucial for emergency-response efforts, as is being certain that the results are real. "Our goal was to have two independent, autonomous, 'gold-standard' assays to provide the highest confidence in detection results in the shortest possible time," says Langlois.

Checking It Twice

As APDS collects air samples, it first runs them through an immunoassay detector. If that detector returns a positive result, APDS performs a second assay based on nucleic-acid amplification and detection. Having two different assay systems increases system reliability and minimizes the possibility of false positives.

The immunoassay detector incorporates liquid arrays, a multiplexed assay that uses small-diameter polystyrene beads (microbeads) coated with thousands of antibodies. Each microbead is colored with a unique combination of red- and orange-emitting dyes. The number of agents that can be detected in a sample is limited only by the number of colored bead sets. When the sample is exposed to the beads, a bioagent, if present, binds to

the bead with the appropriate antibody. A second fluorescently labeled antibody is then added to the sample, resulting in a highly fluorescent target for flow analysis. Preparing the sample and performing this first analysis takes less than 30 minutes.

System software compares the result with preset threshold criteria for a positive identification. A positive immunoassay result triggers the second test—a DNA analysis using the rapid polymerase chain reaction (PCR) technique. For this test, an archived sample is mixed with reagents for the target organism and introduced into the flow-through PCR system, which consists of a Livermore-designed, silicon machined thermocycler mounted in line with the sample preparation unit. Specific nucleic-acid signatures associated with the targeted bioagent are amplified up to a billionfold and detected as a change in fluorescence. The PCR analysis is completed within 30 minutes.

Results are transmitted every hour to a control center, where the instrument's performance is monitored. "The architecture of wireless communication with a command center works well with existing building safety and security systems," says Langlois. "Because malfunctions and failures are rare, a small command staff can easily oversee a network of 10 to 100 instruments and still provide maintenance, scientific interpretation of assay results, and communication with the appropriate authorities."

Saving Time, Saving Lives

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The system can be adapted for situations where environmental or clinical pathogens require monitoring. For example, APDS could test for mold or fungal spores in buildings or for the airborne spread of contagious materials in hospitals. It also could identify disease outbreaks in livestock transport centers or feedlots. "Basically, there are no fully integrated systems with the capabilities of APDS commercially available in the civilian or military market," notes Langlois. "The system offers ongoing environmental monitoring and rapid detection of harmful pathogens, allowing emergency workers to respond immediately to decontaminate areas and, most importantly, save lives."

—Ann Parker

Key Words: anthrax, Autonomous Pathogen Detection System (APDS), biological agents, bioterrorism, multiplex immunoassay, polymerase chain reaction (PCR), R&D 100 Award, ricin.

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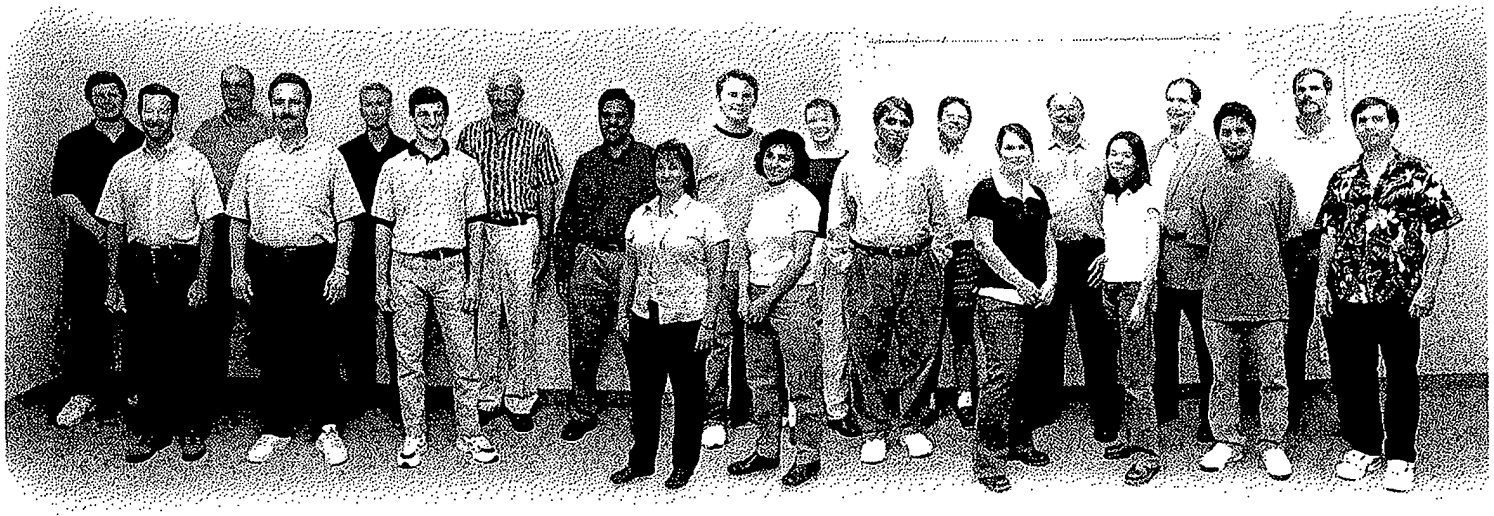

APDS team members: (from left) Anthony Makarewicz, Donald Masquelier, Les Jones, Robert Johnson, Bill Colston, Bruce Henderer, Fred Milanovich, Kodumudi Venkateswaran, Anne Marie Erler, Benjamin Hindson, Shanavaz Nasarabadi, Mary McBride, Ramakrishna Madabhushi, Steve Brown, Sally Marie Smith, Richard Langlois, Dora Maria Gutierrez, Ray Mariella, Ujwal Sathyam Setlur, John Dzenitis, and Tom Metz. Not pictured: Keith Burris.